REMARKS/ARGUMENTS

STATUS OF CLAIMS

Prior to this amendment

Claims 1 and 70-96 were pending and under examination.

Claims 27-28, 36-38, 48-50, 57-59, 63-64, and 66 were withdrawn.

Claims 2-26, 29-35, 39-47, 51-56, 60-62, 65, and 67-69 were cancelled.

In this Document

Claims 1, 70-75, 80, 84, 86, and 95-96 are amended.

Claims 97-111 are added.

SUPPORT FOR AMENDMENTS

Support for recitations added to the claims can be found at the following locations:

Recitation	Claims	Specification[1]
cGMP-specific	1, 27, 36, 49, 57, 63, 70-75, 80, 96, 97, 108, 109	[108] In another invention embodiment, at least one of the administered compounds is a tetracyclic cGMP specific PDE inhibitor such as those described in U.S. Pat. No. 6,143,746 and as set forth in the following Formulae VI-IX including pharmaceutically acceptable salts thereof.
PDE-5	1, 27, 36, 49, 57, 63, 70-75, 80, 96, 97, 108, 109	[0014] We have found that administration of one or more PDE inhibitor compounds, particularly a PDE-5 inhibitor compound such as sildenafil can significantly enhance nucleic acid delivery to targeted tissue.
Wherein the tissue is a solid	1, 27, 36, 96	[0039] As stated above, the

[1] Citations to published application no. 20020094326.

Recitation	Claims	Specification[1]
cell mass selected from the group consisting of a solid organ and a solid tumor		present invention provides methods and compositions that enable effective delivery of nucleic acid to desired cells, including to cells of a solid cell mass, e.g. of an organ such as a mammalian heart or liver, or other solid cell mass such as a solid tumor. [0458] Nucleic acid can be administered to selected tissue by a variety of protocols. The preferred administration method is perfusion of a liquid formulation of the nucleic acid through a solid organ such as a heart or liver or other solid cell mass such as a solid tumor.
Subsequently and/or simultaneously	1, 27, 36, 96	[0469] The one or more permeability agents also may be present in the kit either packaged separately from for later formulation, or pre-formulated with such a low calcium concentration solution for administration prior to delivery of the exogenous nucleic acid. [0479] Following pretreatment, the heart was infected with Krebs buffer containing the pretreatment compound at the stated concentration and Adgal 1 x 10^8 pfu/ml for 2 minutes.
Sildenafil	27, 70	[0004] The present invention relates to improved gene transfer methods and, more particularly, methods that enable highly efficient and widespread delivery of

Recitation	Claims	Specification[1]
		selected nucleic acids, to solid organs such as the heart or liver as well as to other solid cell masses such as a solid tumor. Preferred methods of the invention include treatment of tissue and/or cells for delivery of nucleic acid with one or more phosphodiesterase inhibitor compounds such as sildenafil.
Nitroglycerin and nitroprusside	75	[0022] In preferred aspects of the invention, a vasculature permeability agent in addition to a PDE inhibitor is administered to tissue or cells to be treated with exogenous nucleic acid. Suitable additional, distinct permeability agents include e.g. serotonin and bradykinin. Other suitable additional, distinct permeability agents will include platelet-activating factor (PAF), prostaglandin E.sub.1 (PGE.sub.1), histamine, vascular endothelium growth factor (VEGF), zona occludens toxin (ZOT), interleukin-2 and other plasma kinins in addition to bradykinin. Nitric oxide agonists or promoters (activators) such as nitroglycerin or nitroprusside.
Heart	84	[0030] Nucleic acid administered in accordance with the invention can express a desired therapeutic agent, or may inhibit expression or

Recitation	Claims	Specification[1]
		function of an endogenous gene of a subject. Nucleic acid also may be administered for diagnostic purposes, for example to express a marker protein. In addition to such therapeutic and diagnostic methods, methods and compositions of the invention also may be employed to examine the effect of a heterologous gene on an intact organ such as a subject's heart, to create animal models of disease and to provide mechanistic information regarding various disease states.
Administered orally	110-111	[0486] These data show increased gene delivery to the intact myocardium. Furthermore, increasing the intracellular concentration of the components of the signalling pathway responsible for the permeability effect improves gene delivery. Taking advantage of this understanding of the intracellular signalling pathways responsible for increasing microvascular permeability, it is shown that use of a PDE-5 inhibitor can particularly delivery effects. Since the exposure time required for VEGF, substance P, 8-Br-cGMP, nitroglycerin or nitroprusside is only 2 minutes and the PDE-5 inhibitors can be given orally or intravenously

Recitation	Claims	Specification[1]
		before the procedure, the current innovations dramatically reduce the pretreatment time before gene delivery.
Catheter	98-99	[0463] Nucleic acid can be administered by perfusion by a variety of strategies. Thus, for instance, for an in vivo administration, a catheter delivery protocol can be employed. Such in situ administration can be suitably employed in a procedure solely to deliver the nucleic acid, or in conjunction with a separate surgical procedure such as a peripheral cardiac bypass. A preferred delivery catheter and system is disclosed in WO 9918792A1 (see the figures of that patent publication).
Direct injection	100-101, 106-107	[0468] The invention also provides pharmaceutical kits for treatment of a disorder of a subject. Kits of the invention preferably include a delivery system or device to administer the exogenous nucleic acid such as a catheter as discussed above, an ex vivo administration system such as those discussed above, a syringe for injection administration and the like.
Percutaneous intracoronary delivery	102-103	[007] In one study, percutaneous intracoronary delivery of 10^{10} pfu of adenovirus caused infection in only about one-third of the myocytes in the region

Recitation	Claims	Specification[1]
		served by the target artery
Perfusion of the coronary artery	104-105	[0464] Nucleic acid also may be suitably administered by perfusion through a procedure involving extra-corporal circulation such as performed during coronary artery bypass surgery and aortic valve replacement surgery. In such clinical settings, both arterial and venous vessels can be accessed for delivery, collection and possible recirculation of the perfusate formulation thus targeting gene transfer to the heart and minimizing delivery to remote organs or tissues.

Rejection of Claims 1, 70, 74, and 96 Under 35 U.S.C. § 102(b)

Claims 1, 70, 74, and 96 stand rejected over Goldring U.S. 5,516, 651. This rejection is respectfully traversed.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).

The rejected claims have been amended to specify that the inhibitor is a cGMP-specific PDE-5 inhibitor and that it is administered prior to and/or simultaneously with administration of nucleic acid. In addition, claim 74 has been amended to recite a particular PDE-5 inhibitor, sildenafil.

Goldring teaches administration of IBMX, a non-selective PDE inhibitor to cells after administration of nucleic acid. "COS-M6 cells were transfected with the human

CTR cDNA and then incubated with calcitonin for 20 minutes in the presence of the phosphodiesterase inhibitor, IBMX." Col. 9, lines 47-52, emphasis added.

Thus, Goldring does not teach the method of the present invention because IBMX is not a cGMP-specific PDE-5 inhibitor and because IBMX was not administered prior to or simultaneous with nucleic acid administration. Thus, Goldring does not teach each and every element of the rejected claims.

Withdrawal of this rejection is respectfully requested in view of the amendments to the claims.

Rejection of Claims 1, 70, 74, and 96 Under 35 U.S.C. § 102(e)

Claims 1, 70, 74, and 96 are rejected as anticipated by Linden (US2002/0082240). This rejection is respectfully traversed.

To reject a claim as anticipated, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d (BNA) 1051, 1053 (Fed. Cir. 1987).

Linden is cited as teaching the delivery of nucleic acids to cells in the presence of rolipam, a Type IV PDE inhibitor.

The rejected claims have been amended to recite the use of a PDE-5 inhibitor, *i.e.*, a Type V PDE inhibitor. Linden does not teach the use of such inhibitors. Thus, Linden does not anticipate claims 1, 70, 74, and 96 because Linden does not teach each and every element of the claimed invention.

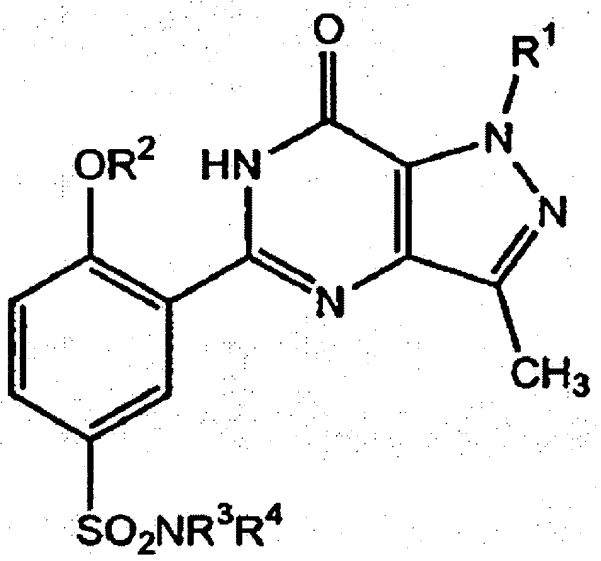
Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 1, 70, 71, 72, and 96 Under 35 U.S.C. § 112, first paragraph

Claims 1, 70, 71, 72, and 96 are rejected as including subject matter which is not adequately described.

The specification allegedly fails to disclose the structures of sufficient species to support the genus of phosphodiesterase compounds originally claimed. The claims have been amended to recite cGMP-specific PDE-5 inhibitors.

In particular, the rejection asserts that the elected core structure pyrazalo [4,3-d] pyrimidin-7-one is only exemplified by one species: sildenafil. However, Formula I at page 12 discloses additional species.



"wherein in Formula I, R1 is methyl or ethyl; R2 is ethyl or n-propyl;

and R3 and R4 are each independently H, or C1 -C6 alkyl optionally substituted with C5 -C7 cycloalkyl or with morpholino; and pharmaceutically acceptable salts thereof."

In addition, one subset of the Formula I compounds is disclosed at page 15, lines 20-25:

"A preferred group of compounds of Formula I above include those wherein:
R3 is H; methyl or ethyl;
R4 is C1 -C6 alkyl optionally substituted with cyclohexyl or with morpholino; and R1 and R2 are as previously defined for formula (I), and pharmaceutically acceptable salts thereof."

Moreover, page 17, lines 17-25, list three additional species:

1-ethyl-5-(5-(n-hexylsulphamoyl)-2-n-propoxy-phenyl)-3-methyl-1,6-dihydroo-7H-pyrazolo[4,3-d]-pyrimidin-7-one;

1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxy-phenyl)-3-methyl-1,6-dihydroo-7H-pyrazolo[4,3-d]-pyrimidin-7-one; and

5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one.

Thus, the specification teaches far more than a single species having the elected core structure.

Formula I was published in WO 96/16657 on June 6, 1996, as were the preferred compounds. See page 3, top half of page, page 7, last paragraph, and page 9, lines 17-25. Thus, this genus of compounds was well known in the art. Moreover, the compounds were known to be cGMP-specific phosphodiesterase inhibitors. See page 2, lines 12-16.

The specification provides working examples of three different cGMP-specific PDE-5 inhibitors which enhance nucleic acid delivery: sildenafil, zaprinast, and T-1032. Although only one of these is in the elected subgenus, this finding demonstrates that the operability of the claimed method is not dependent upon a particular structure, but rather on the ability of the compounds to inhibit PDE-5.

The art was well aware of a number of types of structures which provide PDE-5 inhibition. The specification teaches many of these types of structures. Given the high level of sophistication in the art regarding these structures and their known correlation with PDE-5 inhibition, the applicant's disclosure very adequately describes the elected subgenus, as well as the full genus of cGMP-specific PDE-5 inhibitors. Withdrawal of this rejection is therefore appropriate.

The Rejection of Claims 1, 70-96 Under 35 U.S.C. § 112, first paragraph

Claims 1 and 70-96 are rejected as allegedly broader than the scope of enablement provided by the specification. These claims are said to be improperly broad with respect to the genera of PDE inhibitors, bicyclic heterocyclic PDE inhibitors, and PDE inhibitors having any of five core structures: a pyrazolo[4,3-d] prymidin-7-one, pyrazolo[3,4-d] pyrimidin-4-one, quinazolin-4-one, purin-6-one, and pyrido[3,2-d]pyrimidin-4-one.

This rejection is respectfully traversed.

Applicants have amended all claims to recite "a cGMP-specific phosphodiesterase-5 inhibitor compound." It is respectfully submitted that this amendment obviates the rejection. Many inhibitors of PDE-5 were known in the art and are disclosed in the subject application. It would not require undue experimentation to

select a PDE-5 inhibitor and use it in the present invention. There is no reason to think that the functioning of PDE-5 inhibitors in the method of the claimed invention would be unpredictable. Three different known inhibitors having three different core structures were tested and found effective in the method of the invention. See paragraph 0485.[2] The PTO has put forward no evidence that would lead one of ordinary skill to conclude that all cGMP-specific PDE-5 inhibitors would not work in the claimed methods.

Withdrawal of this rejection is requested in view of the claim amendments.

The Rejection of Claims 1, 70-84, 86-89, 91, and 93-96 Under 35 U.S.C. § 112, first paragraph

Claims 1, 70-84, 86-89, 91, and 93-96 stand rejected as broader than the enablement provided by the present invention. The specification is said to provide enablement only for

- *ex vivo* delivery; and
- direction injection.

Accordingly, claim 85 (administered to a solid organ), claim 90 (administered to a solid tumor), and claim 92 (administered *ex vivo*) were not rejected on this ground. Claims 1 and 96, the only two independent claims, have been amended to correspond to the scope that the Office Action concedes to be enabled. Thus, the recitations of claims 85 and 90 have been incorporated into claims 1 and 96. It is respectfully submitted that this amendment renders all claims enabled with regard to the issue raised in this rejection.

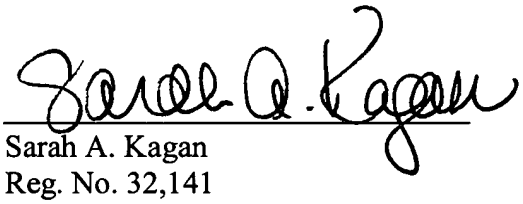
[2] Reference to the published application no. 20020094326.

The Rejection of Claims 75 and 96 Under 35 U.S.C. § 112, second paragraph

Claims 75 and 96 have been amended to address the antecedent basis and clarify other issues raised. Withdrawal of this rejection is respectfully requested in view of the amendments.

Respectfully submitted,

Dated: May 18, 2004

By: 

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